

Lettuce contact allergy

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Summary

Lettuce (*Lactuca sativa* L.) and its varieties are important vegetable crops worldwide. They are also well-known, rarely reported, causes of contact allergy. As lettuce allergens and extracts are not commercially available, the allergy may be underdiagnosed. The aims of this article are to present new data on lettuce contact allergy and review the literature. Lettuce is weakly allergenic, and occupational cases are mainly reported. Using aimed patch testing in Compositae-allergic patients, two recent Danish studies showed prevalence rates of positive lettuce reactions of 11% and 22%. The majority of cases are non-occupational, and may partly be caused by cross-reactivity. The sesquiterpene lactone mix seems to be a poor screening agent for lettuce contact allergy, as the prevalence of positive reactions is significantly higher in non-occupationally sensitized patients. Because of the easy degradability of lettuce allergens, it is recommended to patch test with freshly cut lettuce stem and supplement this with Compositae mix. As contact urticaria and protein contact dermatitis may present as dermatitis, it is important to perform prick–prick tests, and possibly scratch patch tests as well. Any person who is occupationally exposed to lettuce for longer periods, especially atotics, amateur gardeners, and persons keeping lettuce-eating pets, is potentially at risk of developing lettuce contact allergy.

Key words: allergic contact dermatitis; Asteraceae; atotics; Compositae; *Lactuca sativa*; lettuce; occupational; patch testing.

Lettuce (*Lactuca sativa* L.) is a member of the tribe Cichorieae, genus *Lactuca*, of the Asteraceae (Compositae) family of plants. It is an ancient cultivated plant, presumably originating from Egypt, and may be derived from the wild species *Lactuca serriola* L. (1). Previously, the milky juice of wild or poisonous lettuce (*Lactuca virosa* L.) was used as a sedative known as 'Lactucarium' (lettuce opium); today, lettuce is an important vegetable crop (1). The numerous lettuce varieties are cultivated worldwide, and the annual production of fresh-cut lettuce was reported to have increased by 10–20% in all European countries around the millennium (2). In view of the extensive cultivation and consumption of lettuce, contact allergy is rarely reported (1). However, as allergens or

extracts are no longer commercially available, the contact allergy may be underdiagnosed.

The aim of this article is to present current aspects of lettuce contact allergy, based on our own patch test results in the past 17 years and a review of the literature.

Patients, Materials, and Methods

Consecutive Compositae-sensitive patients who had positive patch test reactions to lettuce allergens/extracts/plant material as is and who were tested between February 1998 and February 2015 were included. The patch test materials were placed on the back for 2 days, with Finn Chambers® (Epitest Ltd, Helsinki, Finland) on Scanpor® tape (Norgesplaster A/S, Oslo, Norway; or SmartPractice®, Phoenix, AZ, USA). Readings were performed on D3–D4 and sometimes on D5–D7, according to the recommendations of the ICDRG (3). The older literature was searched by the use of textbooks, supplemented with studies from reference

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Table 1. Patch test reactions in 37 lettuce-sensitive patients

Patient no.	Sex/age (years)	Lettuce reaction	SL mix reaction	Parthenolide reaction	Compositae mix reaction	Occupational allergy
1	F/51	+ oleoresin	—	—	+++	Partly
2	F/77	+ oleoresin	+	++	NT*	No
3	F/30	+ oleoresin, as is	?+—	—	++	Yes
4	F/46	++ oleoresin	+++	+++	+++	No
5	F/42	++ oleoresin	+++	+++	+++	No
6	M/76	++ oleoresin	+++	+++	+++	No
7	F/59	++ oleoresin	++	++	+++	No
8	F/61	++ oleoresin	++	++	++	No
9	F/48	+ oleoresin	+	++	++	No
10	F/58	++ oleoresin	++	++	+++	No
11	F/49	++ oleoresin	++	?+— follicular reaction	++	Possibly
12	F/58	++ oleoresin	+++	+++	+++	No
13	M/74	+++ oleoresin	+++	+++	+++	No
14	F/48	+ oleoresin	—	—	+	No
15	F/51	++ oleoresin	?+— follicular reaction	?+— follicular reaction	+++	No
16	F/34	+ oleoresin	—	—	++	Possibly
17	F/34	++ oleoresin	—	+	++	No
18	F/55	++ oleoresin	?+—	++	?+— follicular reaction	Partly
19	F/41	+ oleoresin	—	—	?+—/+++**	Yes
20	F/54	++ oleoresin	—	—	+	No
21	F/61	++ oleoresin	+++	+++	+++	No
22	F/46	+ oleoresin	++	++	++	No
23	F/55	++ oleoresin	+	?+— follicular reaction	++	No
24	F/56	++ oleoresin	++	++	++	No
25	M/10	+ oleoresin	++	++	++	No
26	F/46	++ oleoresin	—	—	++	No
27	F/48	+ oleoresin	—	—	+	No
28	F/32	+ oleoresin	—	—	++	Possibly
29	F/59	++ oleoresin	++	++	++	Previously
30	F/40	'as is'	—	—	++	Yes
31	F/37	'as is'	++	++	++	Previously
32	F/62	'as is'	+++	+++	+++	No
33	F/39	'as is'	+	—	++	Yes
34	M/57	'as is'	Positive	Positive	NT	No
35	F/48	'as is'	+	—/NT**	—	Previously
36	F/21	'as is'	?+— follicular reaction	—	++	Yes
37	F/63	'as is'	++	++	++	No

F, female; M, male; NT, not tested; SL, sesquiterpene lactone.

*Positive patch test reactions to components of the Compositae mix.

**Compositae mix positive at a later test session.

***Parthenolide NT, but previously negative.

lists in articles, and the newer literature was searched by the use of databases such as MEDLINE/PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), Bota Derma (<http://botaderma.com>), and Botanical Dermatology (<http://www.botanical-dermatology-database.info>).

Clinical Study

In the 17-year period from February 1998 to February 2015, 77 of 325 Compositae-sensitive patients were patch tested for lettuce contact allergy. Thirty-seven of

the 77 patients reacted positively to lettuce: 33 females with a mean age of 49 years, and 4 males with a mean age of 54 years. The youngest patient was a 10-year-old boy, and the oldest was a 77-year old woman. In the majority of the patients (34/37), the lettuce reactions were considered to be of current or old relevance. The distribution of patch test reactions to the sesquiterpene lactone (SL) mix and parthenolide, which were included in the baseline series in the study period, and possibly Compositae mix 5% or 6% are shown in Table 1. Twelve female patients were currently/previously/possibly or

partly occupationally sensitized to lettuce – patient no. 31 had worked with lettuce years ago, but had been non-occupationally sensitized to Compositae prior to testing with lettuce, and was thus not included in the occupationally sensitized patients (Table 1). Their mean age was 42 years, as opposed to 53 years for the 25 non-occupationally sensitized patients. The prevalence rates of positive patch test reactions to SL mix were 33% among the occupationally sensitized patients and 76% among the non-occupationally sensitized patients ($p = 0.03$, Fisher's exact test).

Altogether, 19 patients had a personal history of atopy, including 9 of the 12 occupationally sensitized patients. However, only 13 of the 37 lettuce-sensitive patients were prick tested with lettuce, and 3 had positive reactions: 2 of the 3 were atopics, and all 3 were occupationally sensitized.

Table 2 shows the reactions to lettuce varieties as is in the 10 patients who had positive patch test reactions to plant material. Finally, the clinical features of the 5 occupationally sensitized patients with current relevance are shown in Table 3. The mean age of these 5 women was 34 years. Patients nos. 19 and 30 had a family history of atopy.

In addition to the 37 lettuce-sensitive patients, another 11 patients had positive patch test reactions to chicory oleoresin from Hollister-Stier® (Spokane, Washington, USA). Even though the plant material used in the production was probably *Cichorium intybus* L. (J Hollister-Stier, 2015), the uncertainty concerning this question caused us to exclude chicory-sensitive patients from the present study.

Allergens

The SLs are important taxonomic markers of the Compositae family of plants. In the Cichorieae tribe, a total of 360 SL compounds and their immediate precursors had been reported up to 2008 (4). Lettuce contains both constitutive SLs, such as lactucin, lactucopicrin, and their derivatives, and the SL phytoalexin, which is synthesized in response to microbial attacks (5).

The SLs occur in the latex of the lactifers. Early on, they were described as bitter compounds, and Price et al., in their study of the chemical and sensory characteristics of 25 varieties of lettuce and 6 varieties of chicory, concluded that the major compound contributing to bitterness was the glycoside of lactucin (6, 7). The first chemical study describing lactucin and lactucopicrin was published in the 19th century, and several have followed (6, 8, 9). In addition to lactucin, 11 β ,13-dihydrolactucin, and lactucopicrin,

Table 2. Results of patch testing with lettuce as is in lettuce-sensitive patients

Patient no.	Patch test material	Patch test result
37	Iceberg lettuce stem/water	++
	Iceberg lettuce stem/ethanol	++
36	Iceberg lettuce stem/water	++
	Iceberg lettuce stem/ethanol	++
35	Iceberg lettuce/water	–
	Iceberg lettuce/ethanol	–
	Mini Romaine lettuce stem/water	+
34	Mini Romaine lettuce stem/ethanol	+
	Mini Romaine lettuce stem/water	+++
	Mini Romaine lettuce stem/ethanol	++
	Mini Romaine leaf surface/water	–
	Mini Romaine leaf underside/water	–
	Mini Romaine leaf surface/ethanol	–
	Mini Romaine leaf underside/ethanol	–
	Iceberg lettuce leaf surface/water	++
	Iceberg lettuce leaf underside/water	++
	Iceberg lettuce leaf surface/ethanol	?+– follicular reaction
33	Iceberg lettuce leaf underside/ethanol	?+– follicular reaction
	Lettuce leaf surface/water	?+– follicular reaction
	Lettuce leaf underside/water	?+– follicular reaction
	Lettuce leaf surface/ethanol	?+– follicular reaction
32	Lettuce leaf underside/ethanol	++
	Mini Romaine lettuce stem/water	++
	Mini Romaine lettuce stem/ethanol	++
	Mini Romaine lettuce leaf/water	–
	Mini Romaine lettuce leaf/ethanol	?+– follicular reaction
30	Iceberg lettuce leaf/ethanol	–
	Iceberg lettuce stem/ethanol	+
9	Iceberg lettuce/water	–
	Iceberg lettuce/ethanol	–
3	Loose leaf lettuce/water	?+– follicular reaction
	Loose leaf lettuce/ethanol	?+– follicular reaction
	Iceberg lettuce/water	+
	Iceberg lettuce/ethanol	?+– follicular reaction

–, negative reaction; ?+–, doubtful positive reaction.

Mahmoud et al. reported the presence of the germacranolide 3 β ,14-dihydroxy-11 β ,13-dihydrocostunolide and lactulide A in the aerial parts of wild-growing Egyptian *L. sativa* (10). In Japanese plants, lactuside A, macrocliniside A and lactuside C were detected (4). Until the publication of Sessa et al. in 2000, it was often reported that lactucin and lactucopicrin conjugates were glycosides, but analysis of the latex from *L.*

Table 3. Clinical features in 5 patients with occupational sensitization to lettuce of current relevance

Patient no./occupation	Hand eczema	Face	Elsewhere	Comment
3/Managing kitchen assistant	Yes	–	–	Atopic with pulpitis and positive prick test reaction to lettuce
19/Kitchen assistant	Yes	–	Yes	Mainly volar vesicular hand eczema, negative prick test result, including with lettuce
30/Chef	Yes	Yes (chelitis and dermatitis of cheek and chin on ingestion of lettuce)	Yes	Vesicular hand and foot eczema, positive prick test reaction to lettuce
33/Kitchen assistant	Yes	Yes	Yes	Atopic with vesicular hand and foot eczema + widespread, negative prick test result with lettuce
36/Café manager	Yes	Yes (possibly lip swelling on ingestion of lettuce)	Yes	Atopic with vesicular hand and foot eczema, positive prick test reaction to lettuce

sativa, *L. serriola*, *L. virosa*, and *C. intybus* showed that the conjugates of lactucin, 8-deoxylactucin and lactucopicrin were mainly 15-oxalates (5). In addition to this novel class of secondary metabolites, Sessa et al. also identified two new sulfated compounds in *L. sativa*: 15-deoxylactucin-8-sulfate and 15-*p*-hydroxyphenyl-acetyl-lactucin-8-sulfate (5). The concentration and distribution of the SLs were highly variable, both in different varieties of lettuce and in other *Lactuca* species, and also depended on the stage of plant development, with significant increases on bolting (5). Concerning the biological activity of the SLs, Sessa et al. concluded that there was no correlation between resistance to pathogens and the occurrence of SLs, but that they might be responsible for the bitterness of the latex (5).

Among this array of SLs occurring in lettuce, only two have been proved to be allergenic: lactucin and lactucopicrin (11). Both a short ether extract of lettuce and the pure SLs were found to be relatively weak sensitizers in both animal and clinical studies (11, 12). The fact that lactucin elicited positive patch test reactions and lactucopicrin elicited no patch test reactions in 2 patients, whereas lactucopicrin seemed to be a stronger sensitizer in an experimental study, could not be explained: a long side chain in lactucopicrin might cause steric hindrance, or cleavage in the skin of the same side chain might lead to the formation of a stronger SL residue allergen (11). The structures of lactucin and lactucopicrin are sensitive to ultraviolet irradiation, and, in aqueous solution, lactucin in particular may be degraded rapidly because of photoreactions (11).

Diagnosis

According to Hausen, lettuce contact allergy may be diagnosed by patch testing with lactucin and/or lactucopicrin 1% pet., a short ether extract of lettuce 10% pet., or the plant or the sap as is (1). The first case of lettuce

contact allergy was reported by Rinkel and Balyeat in 1932 in a female salad maker with occupational dermatitis (13). When the patient did not react to a scratch test with lettuce, which was the only method employed by the authors until then, they invented a lettuce contact test by bandaging lettuce on her upper arm (13). Subsequently, positive patch test reactions to lettuce were reported by Morris in a food handler (14), by Krook in a lettuce gardener (15), by Vail and Mitchell in a supermarket produce manager (16, 17), and by Krook in 4 persons, including the above-mentioned lettuce gardener, a lettuce packer in a supermarket, a cold-buffet manager, and a cold-buffet manageress/cook (18). Veien et al., in their study of causes of eczema in 180 persons in food-handling occupations, reported that, although one-third of the persons had positive patch test reactions to either allergens of the baseline series or food items, only 9 had positive patch test reactions to the latter, including 2 to lettuce (19). In 1986, Hausen et al., for the first time, reported the results of patch testing with lactucin and lactucopicrin in 2 persons with occupational lettuce contact dermatitis (11). A female shop assistant, working in the vegetable department of a supermarket, had positive patch test reactions to lactucin and to the leaf and stem of crushed lettuce, whereas a male lettuce gardener did not react to either SL (11). However, scratch chamber tests with lactucin and lactucopicrin, on the volar side of his right arm, gave negative results at 20 min and 48 hr, but a positive result with lactucin at 96 hr, when a papular reaction appeared. Testing with scratch chamber tests applied for 2 days on the volar side of his left arm and the back elicited a 3+ reaction to lactucin and erythema caused by lactucopicrin on the arm, whereas tests on the back gave negative results (11). These peculiar findings were in accordance with the results of previous tests in the latter patient: he had negative patch test results with full-grown crushed fresh lettuce leaf, stem, and sap, and negative scratch chamber

test results with the same materials at 20 min, followed by positive reactions to the milky sap at 48 and 96 hr (20). The sap also caused a positive reaction after 2 days in a repeated open application test (20).

As mentioned above, Hausen et al. could not explain the discrepancy between the positive reactions to lactucin in the 2 patients and the fact that lactucopicrin seemed to be a stronger sensitizer in an experimental animal study (11). Mitchell et al. also reported a positive patch test reaction to lactucin and a negative result with lactucopicrin in an occupationally lettuce-sensitized chef (21). Conversely, Oliwiecki et al., in their study on lettuce allergy in 2 housewives, reported a negative result with lactucin and a doubtful positive reaction to lactucopicrin in the first patient, who had a 2+ reaction to a 10% ether extract of lettuce, and positive patch test reactions to both allergens in the second patient (22). In a study of occupational dermatitis in Danish gardeners and greenhouse workers, none of the 7 persons tested with lactucopicrin had positive reactions (23). On the other hand, in a survey of 190 consecutive Danish Compositae-allergic patients, lactucin elicited positive reactions in 4 of 10 persons tested (40%), and lactucopicrin elicited positive reactions in 5 of 36 persons tested (14%) (24). Altogether, the results support the suggestion by Hausen et al. in 1986 that lactucin is a stronger sensitizer than lactucopicrin in humans (11). In addition to the two Danish studies, in which lettuce contact allergy was also diagnosed by patch testing with plant material as is, oleoresins, and an ether extract, Kanerva et al. also reported positive patch test reactions to lettuce as is (25).

As pointed out by Hausen et al., patch testing with lettuce as is involves a risk of false-negative reactions, because of possible degradation of the allergens (11). This may be supported by the results of this study: in 3 patients, patch testing with lettuce stem elicited positive reactions, whereas patch testing with leaf of the same cultivar gave negative results, and, in another patient, Romaine lettuce stem elicited positive reactions, whereas testing with iceberg lettuce leaf gave negative results (Table 2, patient nos. 30, 31, 34, and 35). This may be explained not only by the use of not entirely fresh, slightly withered leaves, but also by the fact that the amount of the allergenic sap is visibly lower in the leaves than in a freshly cut, oozing stem. Furthermore, fresh young lettuce leaves may contain such small quantities of SLs that they cannot elicit positive patch test reactions. Although the number of patients tested with lettuce as is in this study was small, it seems that patch testing with stem is more reliable than patch testing with leaves. Apparently, the addition of water or ethanol to enhance the allergic reaction in the skin is not necessary for testing with stems, as the

reactions with the two vehicles were similar in most cases. However, a slight dilution may diminish a possible caustic effect of the sap (26). According to Hausen, both lactucin and lactucopicrin are soluble in ethanol, and lactucin is also soluble in water (1). Concerning testing with leaves, the results were not consistent: 2 patients reacted positively to leaf wetted with water and 1 to leaf wetted with ethanol (Table 2). Strongly positive patch test reactions to lettuce leaves have been reported, but the reactions probably reflect the fact that the patients were highly sensitive after occupational exposure (11, 13, 15, 16, 18, 21, 25). Furthermore, Krook reported on a lettuce gardener who only had skin problems after exposure to full-grown plants; this is in accordance with the fact that the concentration of SLs increases on bolting (5, 15). Thus, in order not to miss less sensitive patients, it is recommended to patch test with freshly cut stems from full-grown plants.

In an unusual case series, Shum and English reported on probable lettuce sensitization without patch testing with lettuce: 6 food handlers, whose single common feature was the handling of lettuce, had positive patch test reactions to Compositae mix 6% pet., but negative results with SL mix (27). In 4 of the 6 patients, the dermatitis resolved on avoidance of lettuce, suggesting that lettuce was the primary sensitizer (27). These results are in accordance with the patch test findings in the present study and a previous study from our department: the prevalence of positive reactions to SL mix is significantly lower in occupationally exposed patients, in whom lettuce is more likely to be the primary sensitizer, than in non-occupationally exposed patients, in whom the positive reaction to lettuce may be caused by cross-reactivity (24). Addition of parthenolide to the baseline series did not increase the rate of detection of lettuce allergy much, as the reactions to SL mix and parthenolide were mostly similar (Table 1). Thus, it is recommended to patch test with Compositae mix in addition to fresh lettuce when contact allergy to lettuce is suspected. The results also justify the suggestion by Jacob et al. to include a lettuce allergen (lactucopicrin) in a new SL mix (SL mix II) (28).

In connection with the studies on contact allergy to lettuce, a number of authors have reported concomitant or isolated immediate lettuce reactions in patients who presented with dermatitis (13, 18, 19, 29–32). In cases of concomitant immediate and delayed sensitization, the patients often had clinical features of both dermatitis and contact urticaria (13, 29). However, it is well known that lettuce may induce contact urticaria, and that repeated episodes of contact urticaria may cause dermatitis (33). Fregert and Sjöborg presented 2 middle-aged females with slight and long-standing severe hand eczema, respectively, who developed summer-related cheilitis and

dermatitis around the mouth. Both patients had positive prick test reactions to lettuce, and the first patient had negative patch test results with lettuce at D2, whereas the second patient was not patch tested (30). Avoidance of lettuce resulted in complete cure in the first patient, and the disappearance of facial symptoms and improvement of the hand eczema in the second (30). There was no information on atopic diathesis for either of the patients (30). Of course, it is possible that the patch test gave a negative result because of poor quality of the lettuce used for testing, but another possibility is that the immediate allergy, which is caused by proteinaceous allergens, presented as dermatitis or exacerbated a pre-existing dermatitis (34, 35). On the other hand, Oliwiecki et al. reported 2 similar cases in middle-aged females with long-standing hand dermatitis; the first patient noticed that eating lettuce caused lip and facial swelling, and the second described burning of the mouth, eczema around her lips, and exacerbation of her dermatitis after eating lettuce (22). Both patients had positive patch test reactions to lettuce or a lettuce allergen, but prick tests were not performed (22). Two of the patients in the present study, patients nos. 30 and 36, developed cheilitis/dermatitis around the mouth and lip swelling, respectively, after eating lettuce, and both had positive patch and prick test reactions to lettuce. One was an atopic, and the other had an atopic half-brother (Table 3). The variation in test procedures in the different studies makes it difficult to draw reliable conclusions, but, in cases of cheilitis and dermatitis periorally in persons with suspected lettuce allergy, it seems to be a good idea to perform patch testing and prick testing with fresh plant material.

Originally, protein contact dermatitis (PCD) was defined as dermatitis caused by a proteinaceous substance that elicited positive immediate test reactions, but often negative delayed test reactions (36). PCD typically presents as hand eczema. Alonso et al. reported a case of occupational PCD caused by lettuce in a 25-year-old female who worked with fruit and vegetables in a supermarket and developed eczema of the fingers, forearms, and face (31). She had positive prick test reactions to, among other things, extracts of lettuce stem, leaf, and sap, but negative patch test results with the same extracts. Positive histamine release test results and the detection of specific IgE antibodies to the sap suggested immediate-type allergy to at least this part of the lettuce plant (31). Escudero et al. also reported a case of PCD caused by lettuce, chicory and endive in a young female who worked in a grocery store (32). She had both mucosal symptoms and chronic eczema, and, in accordance with this, she had positive prick test reactions to

fresh lettuce, chicory, and endive, and a positive vesicular reaction to the same plants at readings after 20 min, but also after 24, 48, 72 and 96 hr (32). The laboratory tests suggested IgE-mediated allergy. Thus, two kinds of immediate reaction and a delayed type of reaction to lettuce coexisted in this patient, which emphasizes the importance of applying more than one kind of test procedure (32). As mentioned above, Helander reported on a lettuce-sensitive gardener who reacted positively to lettuce sap in scratch chamber tests after 48 and 96 hr, but had negative results with patch tests; apparently, it was necessary to test in previously affected skin, which was also slightly injured prior to testing (11, 20). Systematic investigations with patch and prick tests with fresh lettuce in normal and previously affected skin, in atopics and non-atopics, are warranted in order to determine the best way to diagnose lettuce contact allergy. Until they are available, it is suggested to patch test with full-grown lettuce stem, freshly cut, and to apply water or ethanol to avoid the irritant effect of the sap. If there is no reaction, a scratch patch test on previously affected skin should be performed, with readings after 20 min and after 2–4 days. It is always recommended to perform prick–prick tests with the same plant material. Furthermore, it is suggested to patch test with a *Compositae* mix in addition to the SL mix.

Prevalence

Epidemiological studies on the prevalence of lettuce sensitization are not available. Obviously, the majority of the older literature consists of mostly occupational case reports or small case series (11, 13–18, 20–22, 25, 27, 29). An exception is the study of Veien et al. on the test results in 180 patients with food-handling occupations: 2 of 9 patients with positive patch test reactions to food items as is reacted positively to lettuce, and 'a few' reactions to lettuce were recorded in 25 persons who were scratch tested with extracts of and/or fresh food (19). In another study on occupational dermatitis, 250 gardeners and greenhouse workers, selected through a questionnaire, were patch tested, and 25 were *Compositae*-sensitive (37). Seven of the 25 persons were diagnosed with occupational and 2 with non-occupational allergic contact dermatitis caused by lettuce, and lettuce was the third in the top 3 ranking of suspected primary sensitizers (37). This is, of course, an extremely selected group of gardeners and greenhouse workers, as the postal questionnaire was originally sent to 1958 persons (38). Results from patch test clinics/dermatology departments are also based on a selected group of eczema patients, but, nevertheless,

they may be the best 'markers' of the importance of a particular contact allergy. In a Danish study on 190 Compositae-sensitive patients, tested in an 8-year period from 1990 to 1998, 42 of 72 tested (58%) were diagnosed with lettuce contact allergy: 12 were occupationally sensitized or had occupational lettuce dermatitis, and 30 were non-occupationally sensitized (24). In the latter group, the relevance of the lettuce allergy was unknown in 13 persons (24). The overall minimum prevalence was 42 of 190 (22%). In the present study, 77 of 325 Compositae-sensitive patients were tested on suspicion of lettuce contact allergy, and 37 (48%) had positive patch test reactions. The overall prevalence was 37 of 325 (11%). This is a minimum figure, as patients with positive reactions to chicory oleoresin were excluded, which was not the case in the previous study (24). Although both lettuce plants and the individual allergens are weak sensitizers, the results suggest that the prevalence of lettuce contact allergy is not negligible (1, 12, 24). In contrast to previous reports, the majority of reactions occur in non-occupationally exposed patients, and even though they may represent cross-reactions, they are often considered to be relevant, perhaps because lettuce is a common vegetable in most households. Screening for this allergy with commercial allergens is not possible, but, as mentioned above, Compositae mix seems to be a better screening agent than the SL mix.

Persons at Risk

Any person engaged in cultivation, harvesting, packing, retail trading or food preparation involving lettuce is potentially at risk. Thus, the literature reports sensitization in gardeners and greenhouse workers (15, 23), a lettuce packer (18), a greengrocer (17), a produce manager (16), a shop assistant in the vegetable department of a supermarket (11), a food services advisor, a kitchen assistant, chefs (27), cold-buffet managers (18), salad makers (13, 29), a restaurant keeper (25), and food handlers in general (14, 19). Furthermore, lettuce sensitization has been reported in non-occupationally exposed persons (30). In the present study, a large proportion of the lettuce-sensitive patients are atopic, and this or an atopic diathesis have also been occasionally reported previously (18, 21, 27). Kitchen work is wet work, and the development of occupational irritant hand dermatitis in atopic individuals may pave the way for lettuce sensitization in this group of persons. At the same time, their risk of acquiring PCD or IgE-mediated allergy to lettuce is probably higher. Hobby gardeners growing lettuce and persons keeping lettuce-loving pets such as rabbits, guinea-pigs and turtles may also be included in the risk group.

Clinical Features

The clinical features of lettuce contact dermatitis are best evaluated in those who are occupationally sensitized, as lettuce is rarely the primary, let alone the only, sensitizer in non-occupationally Compositae-allergic persons.

Krook described work-related dermatitis of the hands, face, arms and legs in a non-atopic greenhouse gardener who cultivated lettuce (15, 18). The hand and arms or hands/arms and face/neck were the sites most often affected in 18 gardeners with occupational Compositae dermatitis (23). The widespread dermatitis in Krook's gardener probably reflects the working conditions, with close manual contact with lettuce in a confined space, which may have been polluted with lettuce sap. On the other hand, persons who handle lettuce in shops or kitchens seem to have primarily dermatitis of the hands and forearms, and rarely facial involvement (11, 13, 16–19, 21, 25, 27). This is also reflected in the present study, even though the clinical aspects were described in 5 persons only; they all worked in kitchens, and their main complaint was hand eczema (Table 3). Four of the 5 patients had, at least partly, volar vesicular hand eczema, with transient plantar involvement also being present in 3, and all had either a personal or a probable family history of atopy. Guillet et al. pointed to an association between atopy and pompholyx, although this could not be confirmed in a previous Danish study, but they also described a 'contact pompholyx', which was more frequent than pompholyx triggered by interdigital–plantar fungal infection or endogenous nickel (39, 40). The positive prick test reactions to lettuce may be in accordance with the atopy/atopic diathesis in the patients. The low mean age, the high prevalence of atopy, the main clinical features of hand eczema and the positive reactions to Compositae mix rather than SL mix are in accordance with the findings of Shum and English (27). Thus, it seems to be especially important to patch (and prick) test with lettuce and Compositae mix in young atopic food handlers with hand eczema.

In the present study, the majority of the patients were not occupationally sensitized to lettuce. Their clinical features are more likely to reflect contact with other Compositae plants and non-related contact allergens. However, 1 of these patients reported that ingestion of lettuce or chicory induced not only perioral dermatitis and swelling of the lateral aspects of the tongue, but also exacerbation of pre-existing eczema or – if the eczema had resolved – induction of eczema corresponding to previously affected sites (41). This discrete systemic reaction may be more prevalent in patients with chronic relapsing dermatitis than is generally thought. An

incognito lettuce dermatitis should be kept in mind when Compositae-allergic patients are treated.

Cross-Reactivity

Among the known allergenic lettuce SLs, lactucin in particular has been detected in various Compositae species, and thus may cause (false) cross-reactions. As mentioned above, lactucin is present in cultivars of *L. sativa*, although in varying amounts. Lactucin also occurs in an array of other *Lactuca* species: *Lactuca floridana* Gaertn. (woodland lettuce), *Lactuca quercina*, *Lactuca saligna* (narrow-leaf lettuce), *L. serriola* (prickly lettuce), *Lactuca tatarica* (blue lettuce), and *L. virosa* (wild or poisonous lettuce) (4). Lactucin and lactucopicrin also occur in *C. intybus* and in the cultivated variety *C. intybus* var. *foliosum* Hegy (Belgian endive, whitloof chicory) and in *Cichorium endivia* L. (endive) (4, 11). Furthermore, lactucin has been detected in *Cichorium pumilum* (wild endive) and *Cichorium spinosum* (4). According to Hausen et al., lactucin and lactucopicrin have also been detected in the weed autumnal dandelion [*Leontodon autumnalis* L., syn.: *Scorzonoides autumnalis* (L.) Moench], but Zidorn mentions only lactucin derivatives crepidiaside A and B (4, 11).

Other lactucin-containing plants include *Cicerbita alpina* (L.) Wallr. (Alpine blue sow-thistle), *Ixeris chinensis* Nakai, *Launaea tenuiloba* Muschl., *Picris hieracioides* L. var. *japonica* Regel, and *Reichardia tingitana* (L.) Roth var. *orientalis* (L.) Asch. & Schweinf. (4).

In both experimental and clinical studies, however, true cross-reactions between lettuce and other Compositae plants occur occasionally (1, 12). This is the most likely explanation for the positive reactions to Compositae mix in occupationally exposed persons in this study.

Prevention

Persons in food-handling occupations with prolonged exposure to lettuce sap should wear gloves. Likewise, Compositae-allergic patients should be encouraged not to handle lettuce and related vegetables without gloves. Information on cross-reacting Compositae species is also important, especially concerning the choice of foliage

vegetables for salads: leaves of non-Compositae plants such as spinach, rocket-salad and Chinese cabbage are safe alternatives.

Conclusions

In accordance with the fact that lettuce plants and their allergens, lactucin and lactucopicrin, are weakly allergenic, most of the literature reports occupational cases or small case series. Using aimed patch testing with lettuce in Compositae-allergic patients, two more recent Danish studies have shown minimum prevalence rates of positive lettuce reactions of 11% and 22%. Most of these reactions are non-occupational, and may, at least partly, be caused by cross-reactivity with other Compositae plants. As commercial lettuce allergens or extracts are not available, the diagnosis of lettuce contact allergy may depend on cross-reactions. In the latest Danish study, the prevalence of positive reactions to the SL mix was significantly higher in non-occupationally sensitized patients than in occupationally sensitized patients, supporting the previous findings showing that Compositae mix is a better screening agent than SL mix for lettuce contact allergy. Patch testing with lettuce as is carries a risk of false-negative reactions, because of the easy degradability of the allergens. On the basis of the latest results, it is recommended to patch test with freshly cut stems, and not leaves, of lettuce, and to apply water or ethanol to avoid a possible caustic effect. If there is a negative patch test result, a scratch patch test with the same plant material on previously affected skin with readings after 20 min and 2–4 days is recommended. In parallel with the reports on delayed reactions to lettuce there is an undercurrent of immediate reactions, and, in occupational cases, prick–prick testing with lettuce is mandatory, as PCD and contact urticaria may present as dermatitis. The clinical features may be dermatitis of the hands and forearms, and possibly more widespread dermatitis in gardeners, and localized hand (and foot) eczema in kitchen assistants. However, persons who are occupationally exposed to lettuce for long periods, and amateur gardeners growing lettuce and persons keeping lettuce-eating pets, are potentially at risk of developing lettuce contact allergy, and should be tested as suggested above.

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